1. INTRODUCTION

1.1. Background

The annual incidence of SCCHN is approximately 40,000 cases per year in the U.S. and 60,000 cases per year in Europe. It is estimated that in the U.S. 12,000 patients will die annually from their disease, and it is estimated that a similar number of deaths may occur in Europe. The key prognostic factor is the stage of disease at presentation. If the patient presents with early disease, as in 25% of new cases, the standard treatment is surgery, radiation, or the combination of both. Long-term disease-free survival is approximately 70%. In this population, patients are more likely to die from a second primary malignancy (field cancerization) than from local regional disease recurrence. On the contrary, for patients presenting with advanced disease (75% of new diagnoses), the failure rate following front-line therapy reaches 70% and the pattern of failure is primarily local and regional recurrence.[1] Regardless of the disease stage at initial presentation, patients having local regional recurrence invariably experience enormous cancer morbidity. The need for palliation cannot be over-estimated.

To date, surgery, radiation or both are considered the standard treatment for SCCHN. In patients who have failed or are unable to receive additional surgery and radiation, chemotherapy is accepted as a standard approach. Several regimens are available. Weekly methotrexate is considered the conventional therapy with partial response rate $\leq$ 30% lasting two to six months.[2] Cisplatin (CDDP) monotherapy has a similar response rate; although the toxicity is greater than methotrexate monotherapy. The combination cisplatin/fluorouracil (CDDP/5-FU) has also been frequently offered to patients. This regimen had an overall response rate of 11-79% and a complete response rate of 0-27%.[3,4] When weekly methotrexate and CDDP/5-FU were compared, it was found that the overall response rate and time to progression were better with the combination therapy than with the monotherapy. However, there was no significant difference in median survival among all three treatment groups in spite of the substantial toxicity associated with the combination therapy.

The treatment that would clearly offer meaningful clinical benefit to patients with recurrent SCCHN remains to be established, this disease continues to be an area of active research.

Over the past decade, the investigation on the cause of human cancer has identified two categories of genetic events leading to cancer: the loss of a tumor suppressor gene and the activation of a tumor promoter gene. The most prevalent tumor suppressor gene is p53[5]. It encodes a phosphoprotein that binds chromosomal DNA and regulates cell proliferation. In the event that normal p53 function is lost due to mutation or deletion, the cell loses its ability to undergo apoptosis. In the absence of physiological apoptosis, cancer can develop[6,7,8,9].

Mutation in the p53 gene has been detected in approximately 50% of tumors in patients with SCCHN.[10,11] Pre-clinical studies in cell cultures and animal models have shown that by introducing a normal p53 gene into head and neck cancer cells with gene transfer technologies, the cancerous growth of cells derived from head and neck cancers can be reverted.

1.1.1. Ad5CMV-*p53*

An adenoviral vector containing the normal p53 gene (Ad5CMV-*p53*) and the necessary expression cassette has been constructed. Pre-clinical studies have shown that cell lines derived from SCCHN could be transfected by Ad5CMV-*p53*. In these cell lines, wild type p53 encoded by Ad5CMV-*p53* was expressed and apoptosis occurred. In rodent models, tumorigenesis of SCCHN cells was reduced when transfected with Ad5CMV-*p53*, regardless of the presence or absence of mutation in the p53 gene.[12] Several studies also suggested that cells with mutated p53 were more sensitive to Ad5CMV-*p53*, than those cells with wild type p53.

In Phase I studies, in patients with advanced SCCHN, Ad5CMV-*p53* has been administered to patients by intra-tumoral injections on days 1, 3, 5, 8, 10, 12 , every four weeks. Preliminary results have shown that the toxicities associated with Ad5CMV-*p53* are minimal[12]. The toxicities commonly seen as a result of chemotherapy have not yet been reported in ongoing Phase I studies with Ad5CMV-*p53*. Molecular analysis of the tumor biopsies from SCCHN patients receiving Ad5CMV-*p53* have demonstrated expression of the wild type p53 as a result of gene transfer. This observation confirms the feasibility of transgene transfer using Ad5CMV-*p53* in SCCHN as previously predicted based on pre-clinical studies. More importantly, histological examination of the biopsy specimens and surgical specimens have revealed extensive necrosis at sites where Ad5CMV-*p53* was injected suggesting anti-tumor effects.

In summary, the preliminary data from an ongoing Phase I study have demonstrated that Ad5CMV-*p53* administered by direct intra-tumoral injections in patients with recurrent SCCHN is generally well tolerated. Several observations have also been made suggesting possible anti-tumor activity of Ad5CMV-*p53*. Although it has been difficult to measure tumor shrinkage precisely in the majority of study patients by imaging studies, (e.g., CT, MRI), reports by a few patients have suggested clinical responses such as improved tongue mobility, speech clarity, and diminished pain caused by the tumor. Further investigation is certainly warranted in SCCHN where few effective therapeutic options currently exist.

A detailed discussion of the pre-clinical and clinical data can be found in the Investigator Brochure [12].

1.2. Rationale

Early Phase I studies in non-small cell lung cancer and SCCHN using two different treatment regimens have established the tolerability and bioactivity of Ad5CMV-*p53* at the cellular level.

The rationale for this Phase II study is to better assess the clinical activity in recurrent SCCHN as evaluated by objective response rate and time to disease progression. In addition, this Phase II study will study two treatment regimens which are derived from the Phase I experience.